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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,277	03/06/2002	Thomas Ehrhardt	50716	2896

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/070,277	Applicant(s) EHRHARDT ET AL.	
	Examiner Tekchand Saidha	Art Unit 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *9,10 and 14*.
   Claim(s) withdrawn from consideration: *1-8,11-13 and 15-18*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see Advisory Action, attached here. .
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Advisory Action

1. Applicants' amendment after-final filed December 21, 2005, is acknowledged.

2. Claims 1-8, 11-13 & 15-18 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed as per response filed November 29, 2004.

3. Claims 9, 10 & 14 are under consideration in this examination.

4. Applicant's arguments filed December 21, 2005 have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

5. Any objection or rejection of record not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

6. Claim Rejections - 35 USC § 112, first paragraph (Enablement)

Claims 9-10 & 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method (or process) for finding herbicidal active substances by inhibiting the activity of a plant dihydroorotase, comprising producing dihydroorotase recombinantly using the DNA sequence of SEQ ID NO: 1, does not reasonably provide enablement for using any DNA sequence having at least 60% homology to SEQ ID NO: 1 and which encodes a protein having the biological activity of a dihydroorotase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 9-10 & 14 are so broad as to encompass a method of identifying an inhibitor of any dihydroorotase, which is encoded by a DNA having at least

60% identity to SEQ ID NO: 1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of dihydroorotase broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of dihydroorotase of SEQ ID NO : 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any dihydroorotase by modifying the DNA to have a homology of at least 60% to SEQ ID NO: 1, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting dihydroorotase activity; (B) the general tolerance of dihydroorotase to modification and extent of such tolerance; (C) a rational and

predictable scheme for modifying any dihydroorotase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including dihydroorotase with an enormous number of amino acid modifications of the of SEQ ID NO: 2 [as a result of modifying the DNA]. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of dihydroorotase(s) having the desired biological characteristics, and further use in the method for identifying herbicidal compounds is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' arguments:

Applicants point out that in addition to SEQ ID NO: 1 from *S. tuberosum*, on page 2, line 9, DHO from *A. thaliana* is disclosed and this can be used according to the present invention. One of ordinary skill in the art easily would be able to find other DHO sequences, for example from other plant species based on sequence similarity or mutagenesis techniques. Also, functionally unrelated DNA would not fall under the scope of present claim 9. Multienzyme DHO complexes such as those from yeast or *D. melanogaster* also would not be within the scope of claim 9 as they are not plants. DHO clearly is identified as an herbicide target.

Applicants also do not agree that the pending claims are directed to a method using any DHO of certain homology, and the Applicants believe that screening for mutants DHO, used in the method, would be routine for one of ordinary skill in the art and can be done by *in vivo* mutagenesis. One of ordinary skill in the art would not have to undergo undue experimentation to obtain the modified DHO sequence[s]. Use of these sequences is illustrated in Greener et al. (1994).

In sum, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC 112, paragraph, because the claims clearly recite both structure and function.

Applicants' arguments have been considered and found to be persuasive, as far as the written description rejection is concerned, which rejection is hereby withdrawn.

However, Applicants' arguments with respect to the enablement rejection is not found to be persuasive because Applicants have clearly failed to address the key issues of the rejection. In particular the specification does not support the broad scope of the claims which encompass all modifications of any dihydroorotase by modifying the DNA to have a homology of at least 60% to SEQ ID NO: 1, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting dihydroorotase activity; (B) the general tolerance of dihydroorotase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any dihydroorotase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Also Applicants arguments that one of skill in the art can by *in vivo* mutagenesis to obtain modified sequences and with the aid of the works of Greener et al. use the sequences.

In response, Applicants do not explain how one of skill art will choose going about modifying the DNA sequences in order to encode a diverse range dihydroorotase, modified to the extent of 40%, which may be employed in the claimed method. Applicants present no details about the regions of dihydroorotase which can or cannot be modified because of the very nature of protein which may lead to an inactive protein. Thus leading to high unpredictability. Details of other non-enabling factors are explained in the enablement rejection.

The reference of Greener has limited use and does not teach applicability to any gene, is time consuming and expensive and only limited number of random mutants can be generated (*see* page 32, column 1-2), as against modifying a sequence (SEQ ID NO: 1) by 40%.

The rejection is therefore maintained.

New arguments:

Applicants have not presented any arguments which are substantially distinct from that previously presented. Applicants reiterate that screening for mutant enzymes is routine in the art and one skilled in the art can achieve mutations in the genes by *in vivo* mutagenesis using the *E. coli model* of Rupp, W. D. et al. The use of this technique is illustrated by Greener et al. (1994).

Applicants have failed to articulate or explain how the teachings of the cited references would apply to the instant claims involving plant dihydroorotase DNA of SEQ ID NO: 1. Further, the key issues of the enablement rejections A-D, remain unaddressed as pointed out in the previous Office Action.

Applicants argue that *In re Fisher* is not on point with the facts of the instant application and as such, should not be used as a determinative reference, because the instant invention does not recite compound claims for nucleic acid.

Applicants' arguments is not found persuasive because irrespective of whether the claims are drawn to a compound or a method of using the compound, the compound in question being used in the method, must also be enabled, in order be effective in the method. This is further substantiated by *University of Rochester v. G.D. Searle & Co. Inc.* Page 427, wherein, a method patent for treating the side effects of pain relievers is invalid for failing to adequately describe the compound used in the claimed method, the U.S. District Court for the Western District of New York rules. Granting a summary judgment motion, the court reasons that the written description requirement of 35 U.S.C. §112 ¶1 cannot be satisfied by merely providing the desired function of the compound without more detail on the compound's structure, chemical formula, chemical name, or physical properties. The court also stresses the applicability of the written description requirements to the compound used, even though the patent consists of method claims rather than compound claims.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

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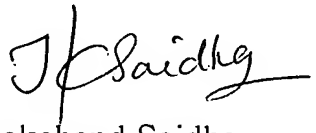

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